

Introduction: Protocol for proposing a mechanism

- ◆ **Formulate a hypothesis to fit the known facts.**
- ◆ **Design and perform (an) experiment(s) to test the hypothesis.**
- ◆ **If the experimental results are consistent with the hypothesis (within the limits of experimental error), proceed to Step 4. Otherwise, return to Step 1.**
- ◆ **If “all” the testable features of the hypothesis have been subjected to experimental scrutiny, then stop. If not, return to Step 2.**

Proposing a mechanism: Points worth noting

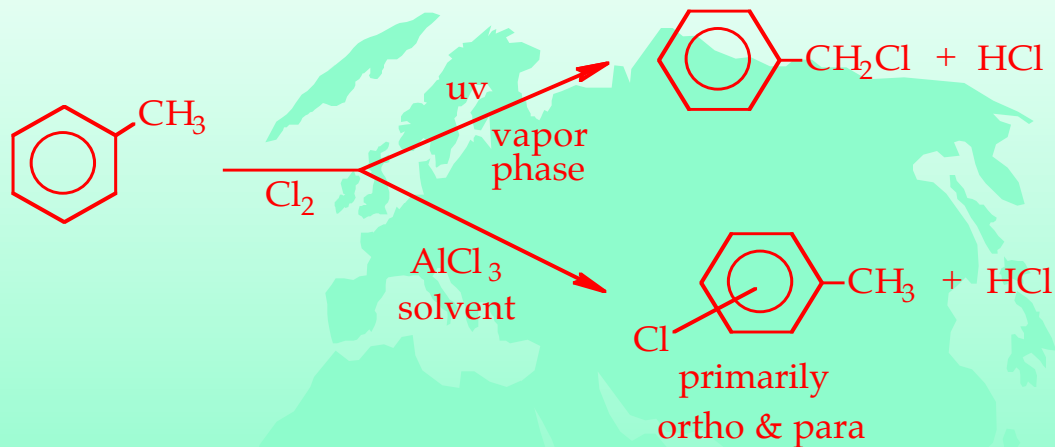
- ◆ It is a misconception that a truly objective scientist gathers all the relevant facts without prejudice prior to formulating a theory. How can one know which facts are relevant unless one has some hypothesis in mind? Objectivity is demonstrated not in collecting facts but in their interpretation.
- ◆ The word “all” in Step 4 presents problems. In pragmatic terms, Step 4 is accomplished when one has sufficient data for a paper or a thesis, when funding for the project runs out, or when the investigator loses interest in the project.
- ◆ One can never get closer to the truth than one’s best guess. That guess can never be proven correct. It can only be proven incorrect!

Minimum criteria a proposed mechanism should meet

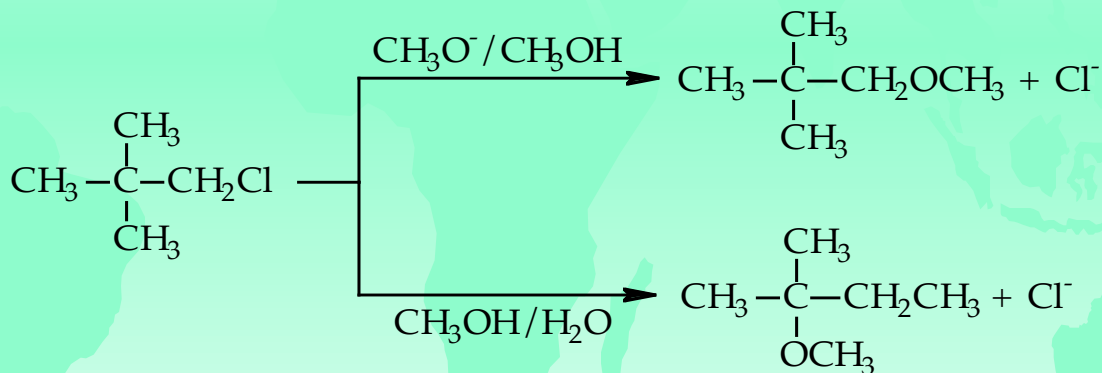
- * It must be consistent with all of the available experimental data.
- * It must make experimentally testable predictions that, if not verified, would prove it false.
- * If several mechanisms are consistent with all the known data, preference is given to the least complicated one.
- * In any multistep mechanism, individual steps should be unimolecular or bimolecular.
- * Each step in a mechanism should be energetically favorable.
- * Each step in a mechanism should be chemically “reasonable”.
- * Where possible, ad hoc additions to a mechanism as devices to explain away inconsistencies with experimental facts should be avoided.

Identification of Reaction Products

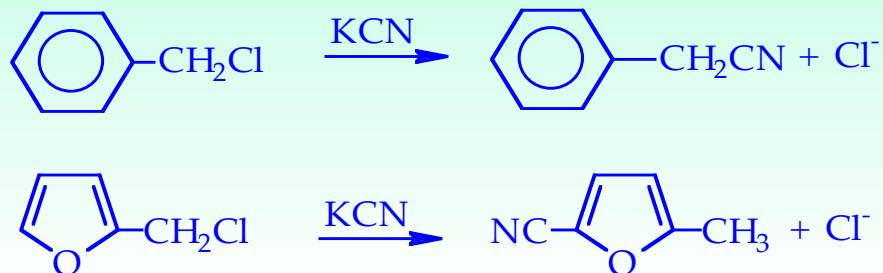
Example I:



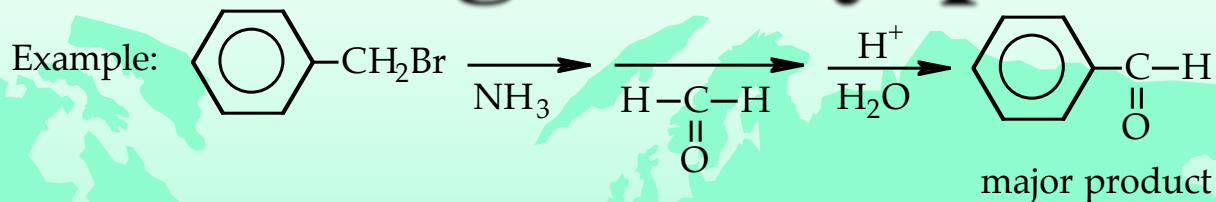
Example II:



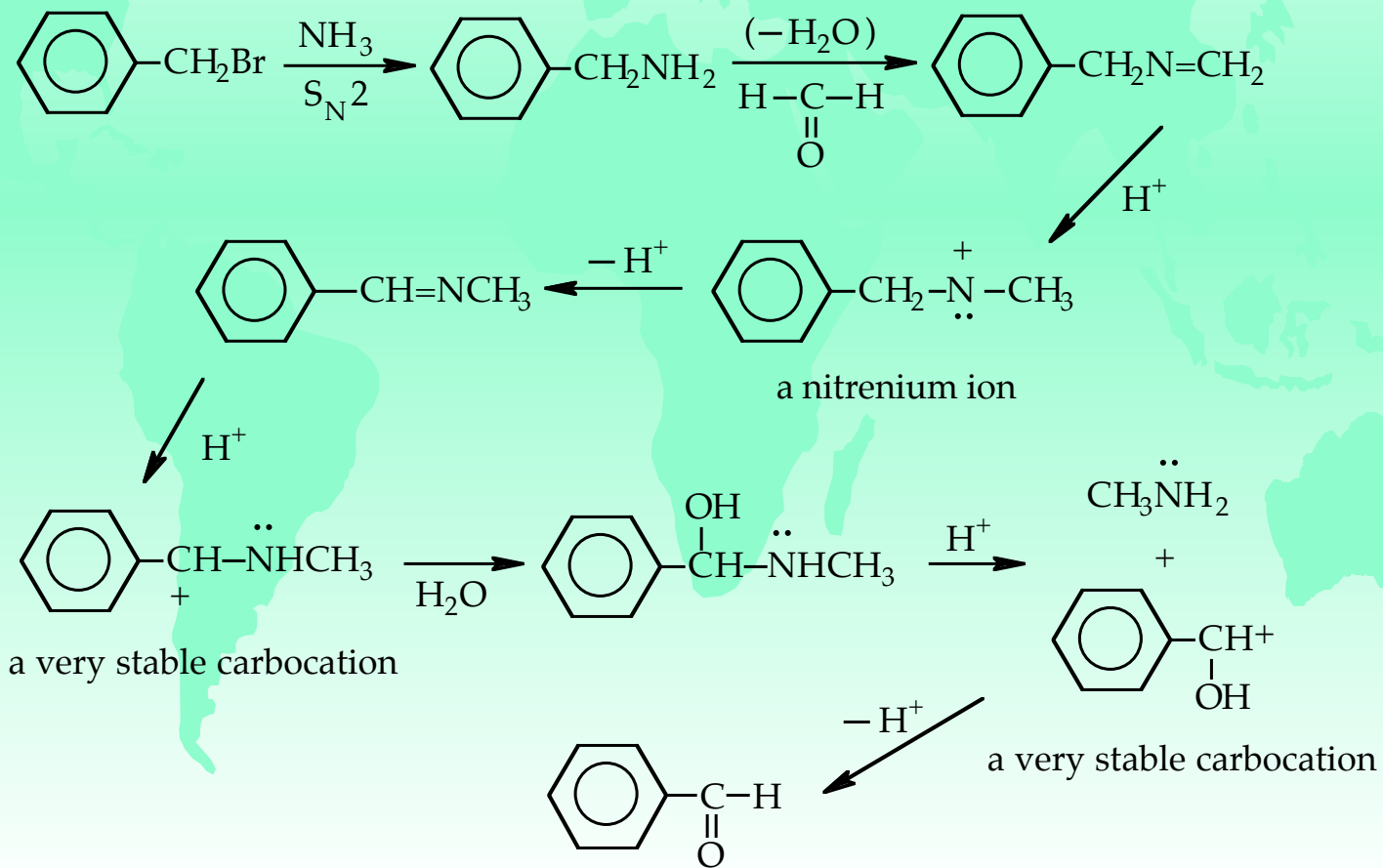
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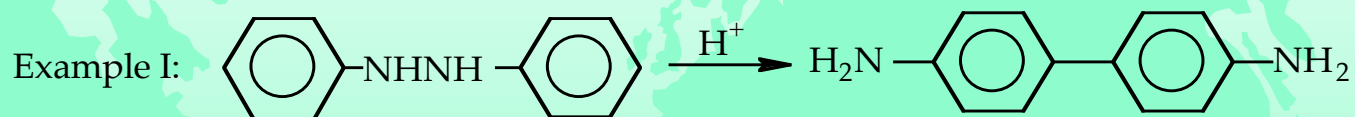
Knowledge of By-products



Plausible Pathway:

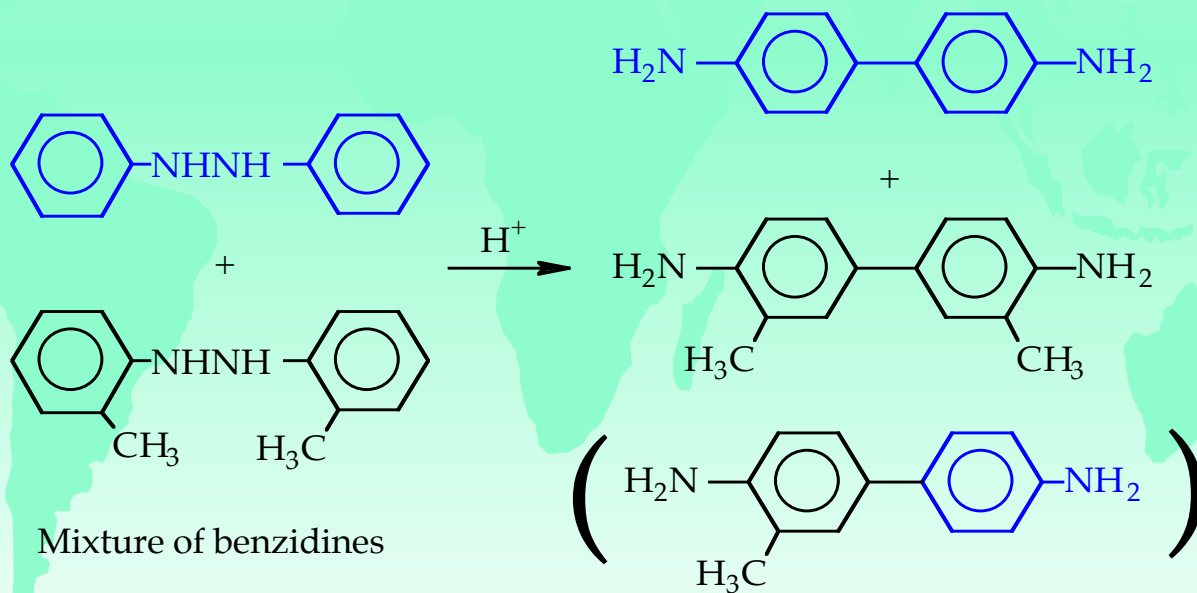


Nonapparent Mechanism despite a knowledge of reaction products

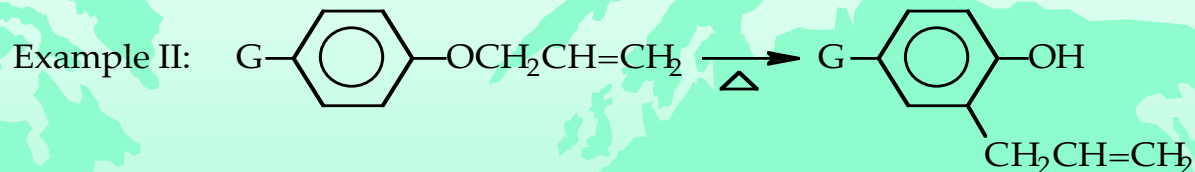


Question: Is the Benzidine rearrangement, shown above, intra- or intermolecular?

Approach: Perform a Crossover experiment



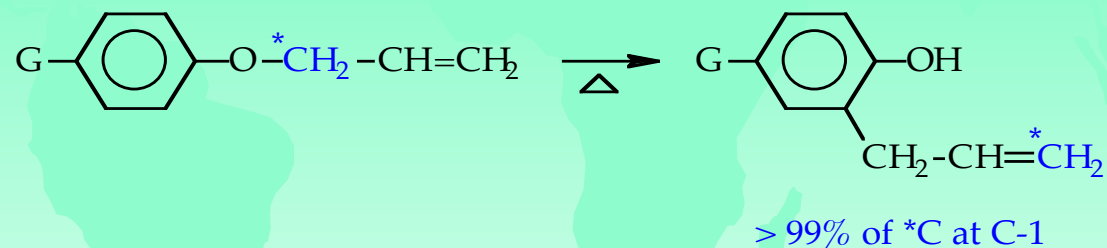
NONAPPARENT MECHANISM DESPITE A KNOWLEDGE OF REACTION PRODUCTS



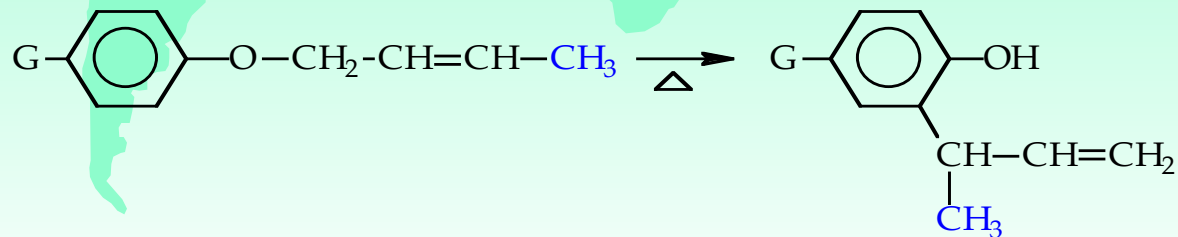
Question: In the Claisen rearrangement, shown above, how did the allyl group migrate from oxygen to the benzene ring?

Approaches that can be utilized:

a) Isotopic labeling study



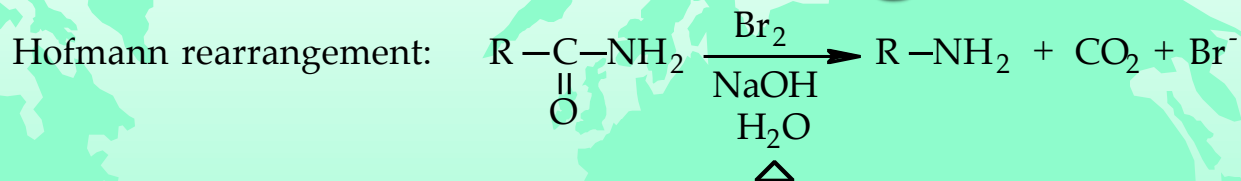
b) Structure modification study



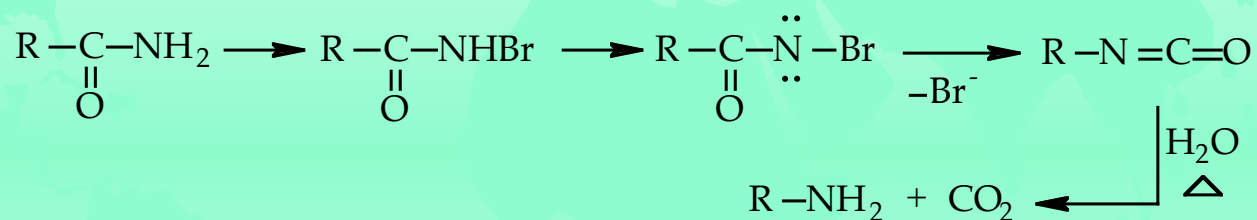
Unresolved question: Is the Claisen rearrangement intra- or intermolecular?

Testing of Isolable Intermediates

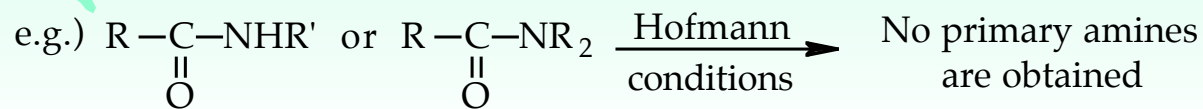
Hofmann rearrangement



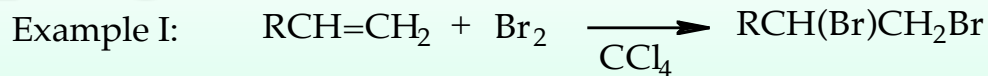
Proposed Mechanism:



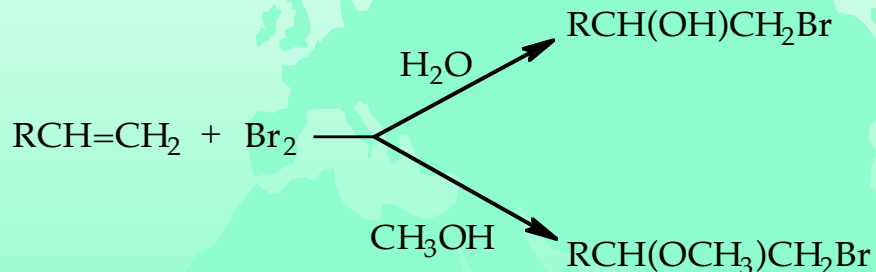
1. If indeed the reaction proceeds in the manner shown above, then any one of the intermediate species, when synthesized independently and allowed to react under Hofmann rearrangement conditions, should yield the same products as the starting amides.
2. If the rearrangement proceeds in the manner shown above, then a structural modification in the starting amide that prevents the formation of any one of the postulated intermediates should also prevent the rearrangement from occurring.



Trapping of Non-isolable Intermediates

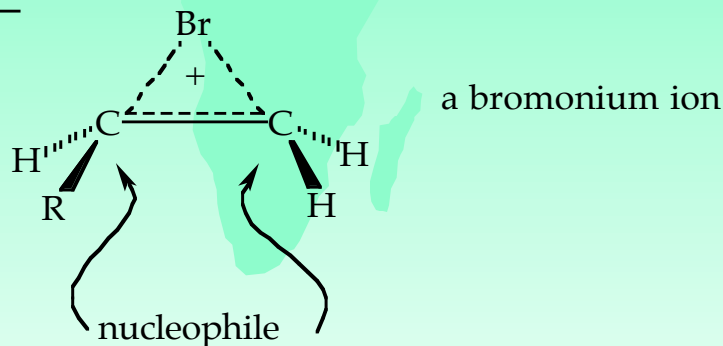


If the above reaction is run in a nucleophilic solvent, the following are obtained as major products:



Conclusion: The addition of Br_2 to a carbon-carbon double bond cannot be a one step process.

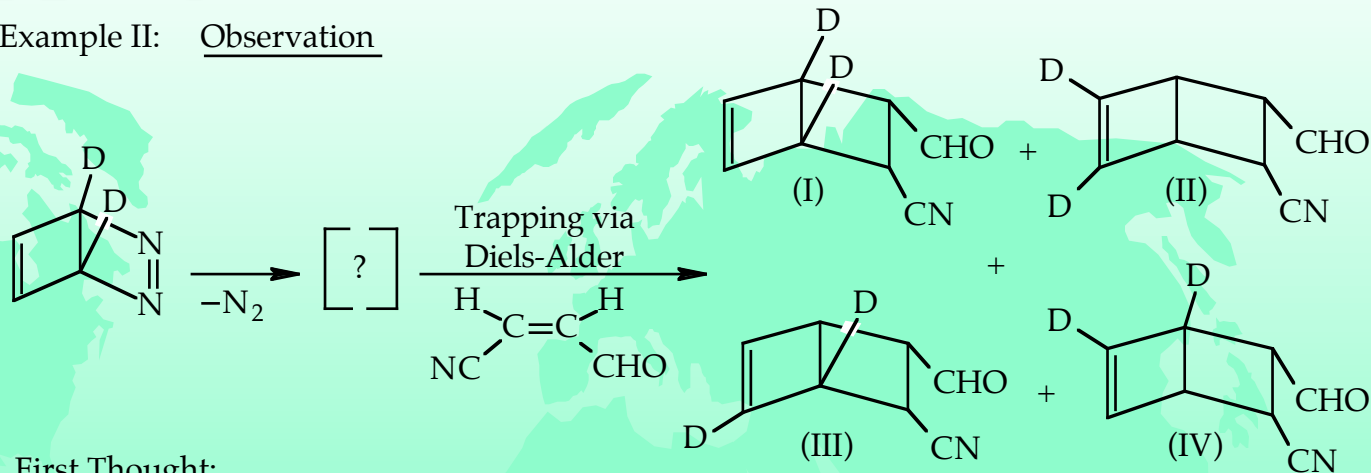
Proposed Intermediate:



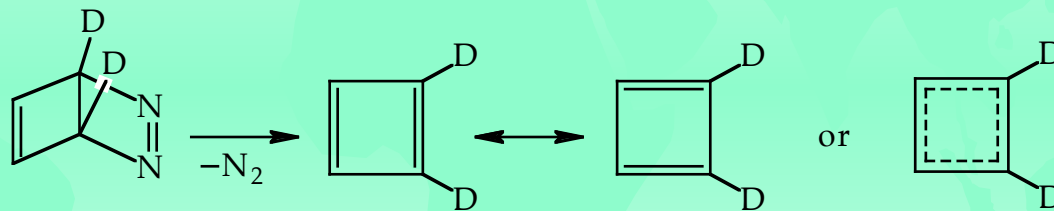
Unresolved Questions: Must the intermediate be a bromonium ion?
Can an open carbocationic intermediate account for the above observations? What additional data would be desirable?

Trapping of Non-isolable Intermediates

Example II: Observation



First Thought:

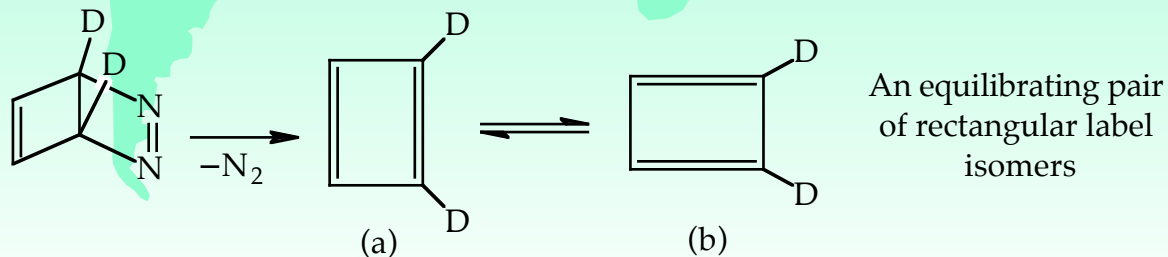


Implications:

For a square cyclobutadiene intermediate, (I) = (II) = (III) = (IV)

Empirical Observation: (I) + (II) \gg (III) + (IV)

Plausible Explanation:

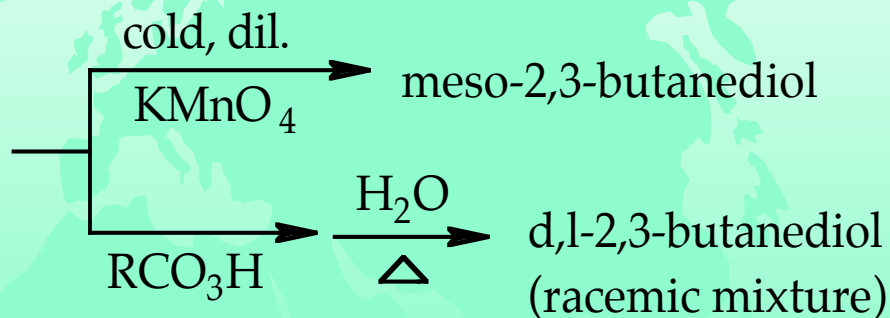
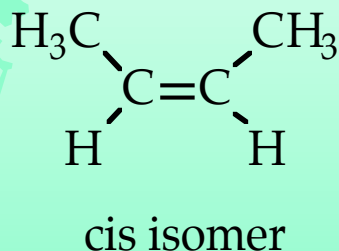


Question: Which label isomer predominates in the equilibrium mixture?

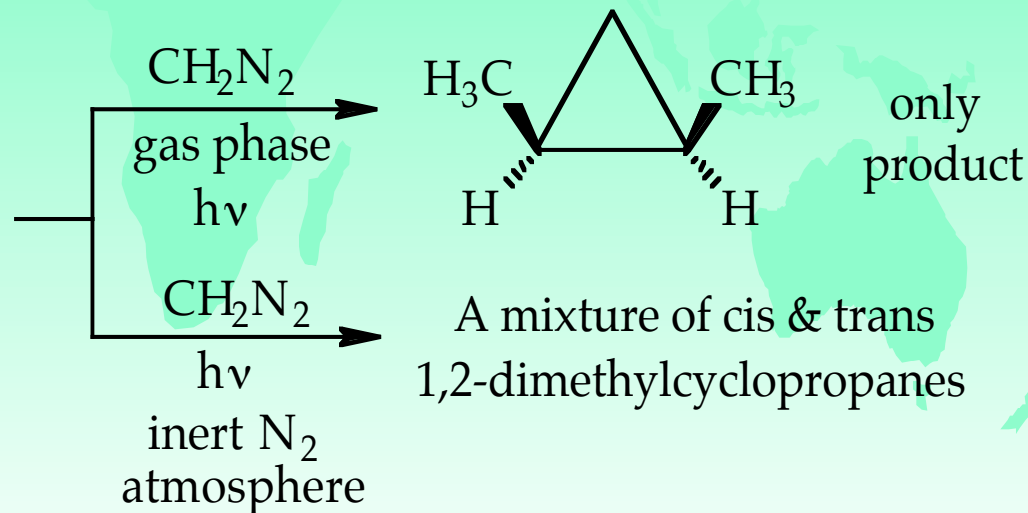
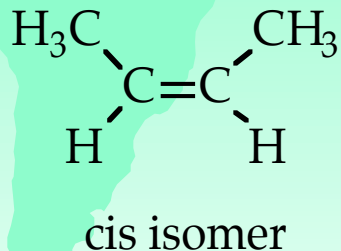
Stereochemical Considerations

Simultaneous vs. Non-simultaneous Addition reactions

Example I:



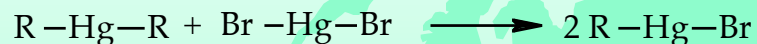
Example II:



Stereochemical Considerations

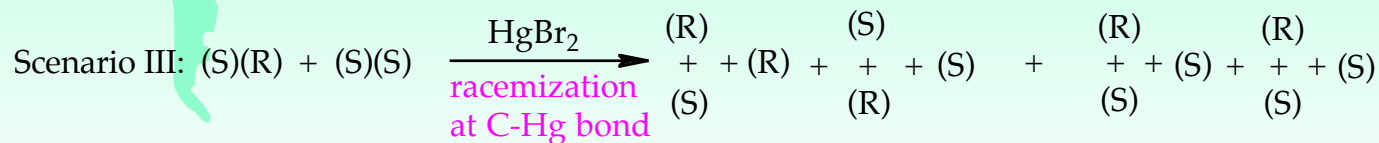
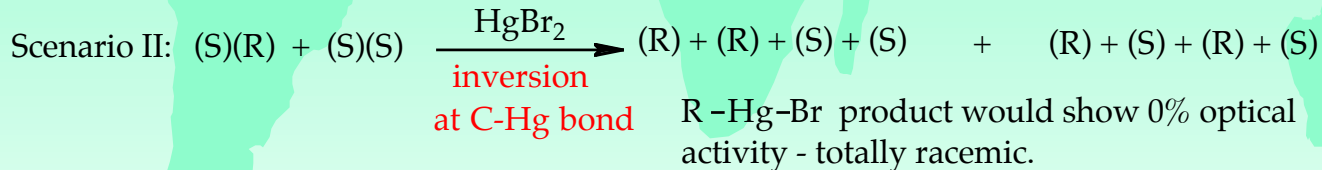
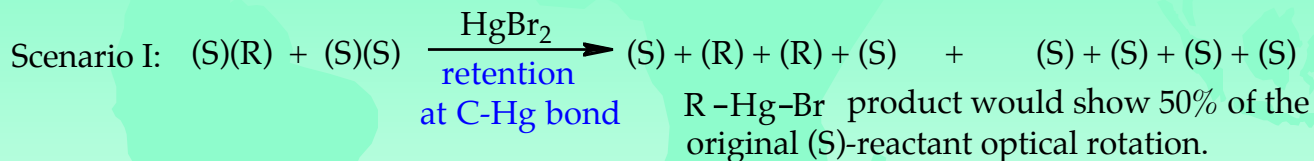
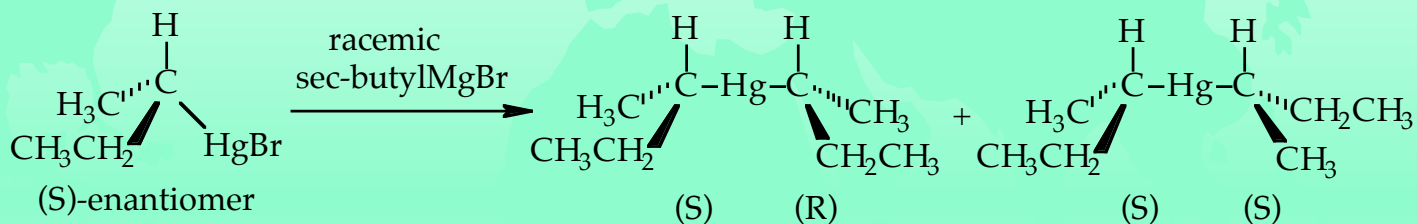
Loss/Retention of Optical Activity

Consider: Conproportionation of Dialkylmercury compounds with mercuric bromide



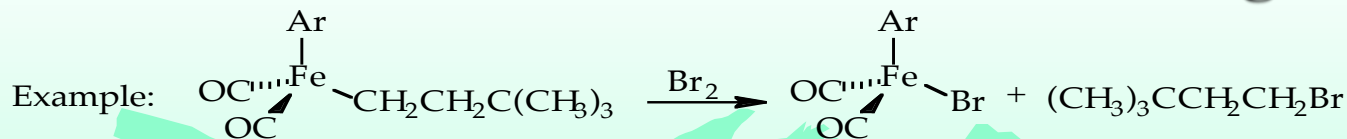
Question: Does cleavage of the carbon-mercury bond occur with **retention of configuration**, **inversion of configuration**, or **racemization**?

Preparation of starting Dialkylmercury reactant:



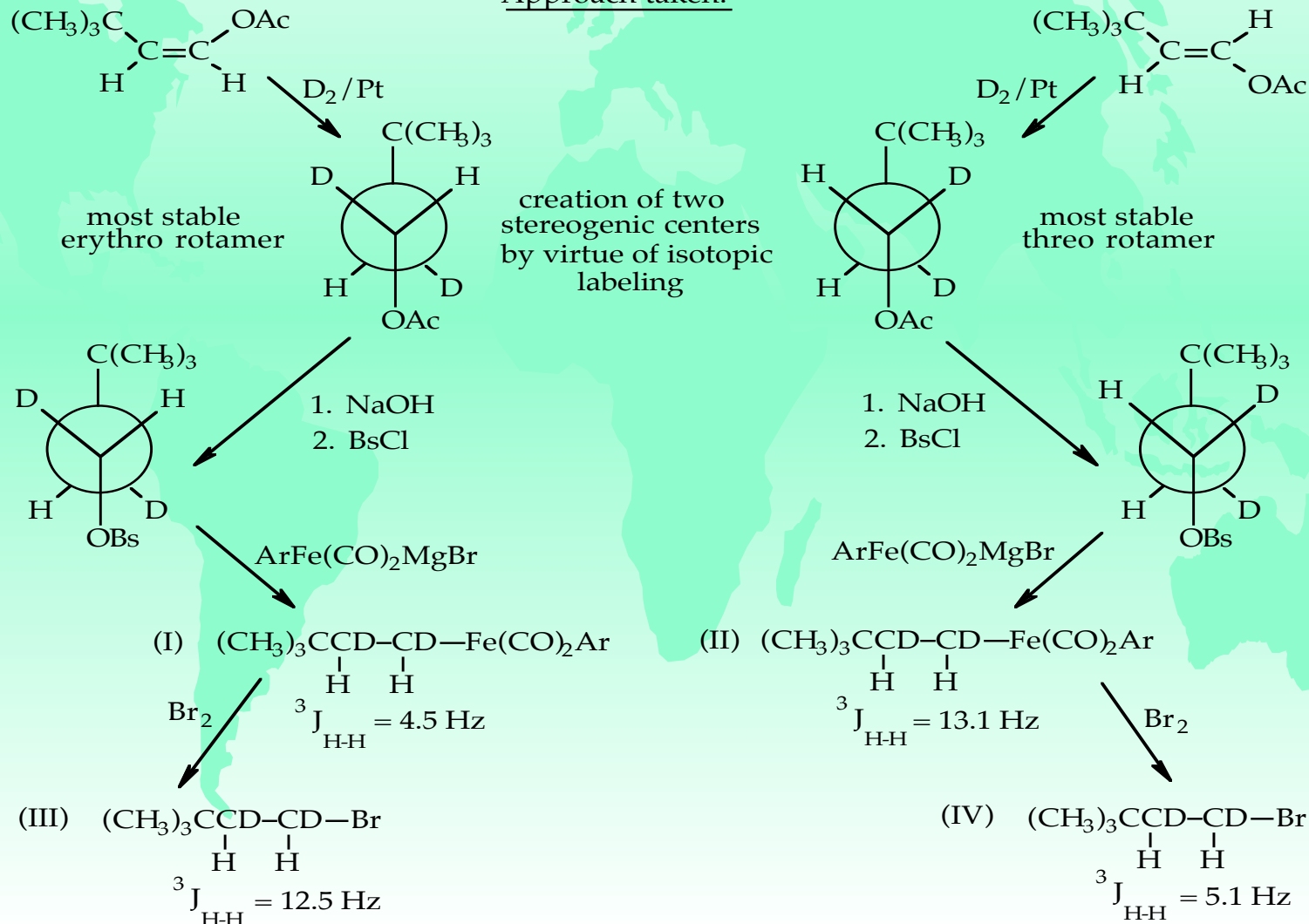
R-Hg-Br product would show 25% of the original (S)-reactant optical rotation.

Stereochemical Considerations: Creation of Stereogenic Centers

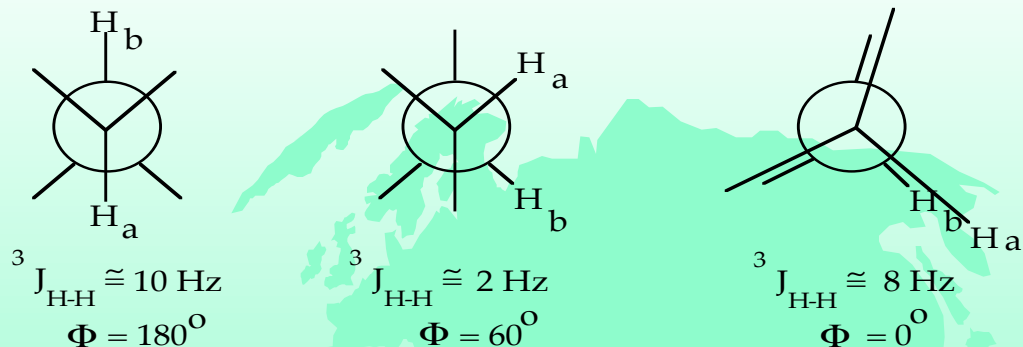


Question: Does cleavage of the Fe-C bond occur with **retention of configuration**, **inversion of configuration**, or **racemization**?

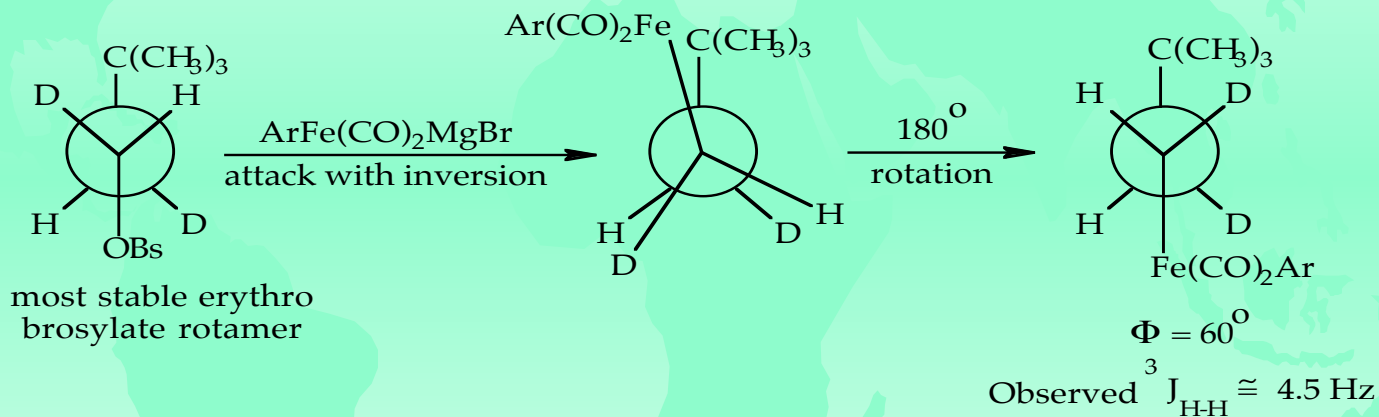
Approach taken:



Point of Information: The Karplus relationship states that vicinal H-H coupling is a function of the dihedral angle that relates the two nuclei.



Conclusion: Fe-C formation occurs with **inversion** of configuration



Conclusion: Fe-C cleavage occurs with **inversion** of configuration

